Fetal Arrhythmias

JANETTE F STRASBURGER, MD
PROFESSOR OF PEDIATRICS AND BIOMEDICAL ENGINEERING
MEDICAL COLLEGE OF WISCONSIN
ATTENDING CARDIOLOGIST, CHILDREN’S WISCONSIN, MILWAUKEE

OCTOBER 21, 2021
Disclosures

- Grants support from NIH (RO1HL143485, RO1HL063174) and the Dr. Scholl Foundation
  - ClinTrials.gov - NCT03775954, NCT03047161

- **SQUID Fetal Magnetocardiography (fMCG)** has FDA 510K clearance for fetal heart recording

- **Optically-pumped Magnetometry (OPM)** is investigational for the fetus

Thankyou to the many families who have participated in this research, and the Fetal Care Centers that refer cases for evaluation
Dr. Wakai, UW Madison Medical Physics Team
- Device Development
- Arrhythmia and LQTS research

Dr. Strasburger Clinical Team - Herma Heart Institute, Fetal Care Center, and MCW/Marquette Biomedical Engineering
Stillbirth Research and rhythm modeling
Fetal Magnetocardiography (fMCG)

940 pregnant subjects have been evaluated since 1998
- Similar to ECG, not MRI
- Real-time interp
- 15-40 weeks GA
- AHA statement 2014, benefits>>risks
- $$$

FHR 68/min
Optically-Pumped Magnetometry (OPM)

84 pregnant subjects since 2015
- Not FDA approved
- 1/10th $ cost
- New superconducting shielding 10X better
Cardiac Monitoring

- Heart rate
- Arrhythmias
- Hypertrophy and signs of chronic strain
- STT abnormalities
- Bundle Branch block
- WPW, and other conduction disturbances
- QT prolongation
  - T wave alternans, J waves, and other repolarization abnormalities
- Medication changes
- Serial assessment
Fetal Monitoring during Labor

Fetal Heart Rate

Maternal Uterine Contractions
Overview

- Tachycardia, bradycardia, and LQTS
  - Who needs treatment?
    - Impact of hydrops fetalis (CHF)
- Antiarrhythmic drugs
  - Indications, administration, PK, and side effects
- Current knowledge gaps, and need for additional research
Fetal Arrhythmias

- Usually 2nd and 3rd trimester
- 1-2% of all pregnancies, mostly benign ectopic beats
  - 10-15% are life-threatening (SVT, Atrial flutter, JET, VT, Torsades de Pointes, Congenital AV block)

Risk factors
- Familial inheritance
- High risk pregnancies
- Nutritional deficiency – Vit D, Mag, Ca, K
- Maternal medications
  - 87% of our subjects were taking medications other than PNV
  - 45% were taking at least one QTc-lengthening drug, and 18% were taking 2 or more. Half were for fetal indications.
Unique Aspects of Fetal Treatment with Antiarrhythmic Drugs

- Fetal arrhythmia therapy is one of the oldest fetal interventions, and one of the most successful, but it is “Off-Label”
- Treatments impact the entire maternal-fetal-placental triad
- High AA drug doses needed to achieve success
- Paucity of means of assessing drug levels for fetus
- Maternal drug levels - slow turn-around, limited availability
Unique Aspects of Fetal Treatment with Antiarrhythmic Drugs

- Over 200 drugs on the market increase the QTc interval
  - Ondansetron, oxytocin, antidepressants, ADHD meds, opioids, etc
- Delay in onset - 5 half-lives to see full effect
- TP transfer influenced by GI absorption, molecular size, protein binding, ionization, by gestation, etc
- Fetal intravascular access has high mortality
  - Intramuscular absorption is good, but risk of sciatic injury
Fetal Tachycardia

- ~1:2500 pregnancies
- Mortality 40-60% without treatment, 0-7% with treatment, unless hydrops, then 10-20%
- Treat if sustained, GA<36 wks, and/or FHR>200/min
  - VT, JET, treat even if rate <200/min
Differences in treatment success between SVT and flutter and between SVT with and without hydrops

Fig. 1. Freedom from termination of fetal SVT vs. AF despite drug treatment (n=111). AF responded more slowly to drug therapy than SVT (HR=2; p=0.005). Cardioversion at 5 and 10 days was achieved in 50% and 63% of fetuses with SVT and in 25% and 41% of cases with AF.

Fig. 2. Freedom from termination of fetal SVT with and without hydrops (n=75). Treatment failure was also more likely if SVT was associated with fetal hydrops (HR=1.8; p=0.04) at the time of diagnosis. It took more than twice as long (9 vs. 4 days) for conversion of 50% of SVT cases to a normal rhythm if fetuses were hydropic. 21% of the hydropic cases died.

Jaeggi et al. Circ 2011;124(16);1746-54
# Transplacental Drugs for SVT and A Flutter

<table>
<thead>
<tr>
<th>AA Agent</th>
<th>F:M drug ratio Route</th>
<th>Efficacy acute and chronic</th>
<th>Intraamniotic accumulation</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin</strong></td>
<td>0.8:1, ↓d if hydrops, PO, IV, fetal IM/IC</td>
<td>50-60%, combined with other AA 80%</td>
<td>Higher, not reflected in [fetal]</td>
<td>N/V, arrhythmias</td>
</tr>
<tr>
<td>NaK ATPase Inhib</td>
<td><strong>Class C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:1( +) PO</td>
<td>60%</td>
<td>27X serum level</td>
<td>CNS, brady, ↑QTc</td>
</tr>
<tr>
<td>Flecainide</td>
<td><strong>Class C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na Chan Inhib</td>
<td>0.9:1(+) PO</td>
<td>50-60%</td>
<td>1.6-28X serum level</td>
<td>CNS, brady, ↑QTc</td>
</tr>
<tr>
<td>Sotalol</td>
<td><strong>Class B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K chan Inhib/B blocker</td>
<td>0.4:1, long T ½ after PO loading; Rare intracordal or peritoneal admin</td>
<td>90+%</td>
<td>Lipophylic, All tissues</td>
<td>Brady; M/F hypothyroidism, ↑QTc, breast feeding CI</td>
</tr>
<tr>
<td>Amiodarone</td>
<td><strong>Class D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-chan Inhib</td>
<td>0.4:1, long T ½ after PO loading; Rare intracordal or peritoneal admin</td>
<td>90+%</td>
<td>Lipophylic, All tissues</td>
<td>Brady; M/F hypothyroidism, ↑QTc, breast feeding CI</td>
</tr>
<tr>
<td>(Adenosine)</td>
<td>NOT Recommended, Dir intracordal admin</td>
<td>LOW</td>
<td>0</td>
<td>Short-acting</td>
</tr>
</tbody>
</table>
Intra-amniotic Drug Accumulation

- Antiarrhythmic agents with intra-amniotic accumulation
  - Sotalol 28:1 [amniotic fluid]/[mat serum]
  - Flecainide 1.6 – 27:1
- Cuneo et al. UOBGyn 2021:57:342-48
  - Reduction in dose using home hand-held Doppler for detection of recurrence
  - Postnatal <40% recurred

Serum and amniotic fluid levels for digoxin and flecainide in 1 subject

From: Takatsuka et al. Clin Case Rep 2021;00:1-5
Fetal AV block

- ~1:10,000 pregnancies
  - Isoimmune SSA-mediated
    - 1-2% of women with lupus, 16% recurrence risk (7.5% after early HCQ)
  - SSA negative with structurally normal heart (LQTS)
  - CHD – AV septum
- Prognosis dependent on etiology
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication/duration Route</th>
<th>F:M drug ratio</th>
<th>Efficacy acute and chronic</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexamethasone</strong> Fluorinated glucocorticoid</td>
<td>PR on echo &gt; 170 ms or AV block onset PO</td>
<td>0.5 F:M, ↓Mab levels</td>
<td>20-40% reversal of 2:1 block, May ↓postnatal cardiomyopathy</td>
<td>Mat HTN, ↑ glu, wt gain, osteopor, etc. Trf breast milk</td>
</tr>
<tr>
<td><strong>IVIG</strong> Anti-inflammatory, Blocks F2/FAB receptors in placenta</td>
<td>Hydrops IV</td>
<td>0.5-1.0:1</td>
<td>in HF, ↓’d mortality from 80-25% $$$ - preapproval needed</td>
<td>Allergic Rxn, Vaccines</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine</strong> TLR blocker, ↓ Endosomal pH</td>
<td>Prior infant with NLE PO</td>
<td>1.04:1</td>
<td>↓’d Heart Block risk from 16 to 7%</td>
<td>↑QTc</td>
</tr>
<tr>
<td><strong>Terbutaline</strong> Beta Agonist</td>
<td>FHR&lt;50/min, if CHD &lt;55/min PO</td>
<td>1-1.5:1</td>
<td>↑ FHR by 5-10 beats/min, Not proven to ↑ survival</td>
<td>↑ mat HR, arrhythmia, CNS</td>
</tr>
</tbody>
</table>
Long QT Syndrome (Inherited Arrhythmias)

- 1:2000
- Very underrecognized, since 40% or more of cases are de novo (fetus as proband)
- Unexplained stillbirth (3-8%)
- 5-10% of SIDS
- Sinus brady, AV block, and Torsades de Pointes (TdP)
FMCG Visit 1, Mat LQTS 2: 29 6/7 wks GA
FMCG Mat LQTS2, Visit 1: 29 6/7 wks GA
Torsades de Pointes in the Fetus

- 7/9 were not recognized by fetal echocardiography
- TdP can appear slow, mimicking sinus rhythm
- Hydrops
- Denovo LQTS accounts for majority, 45% mortality
- Familial LQT2 or 3 or rare variants
  - No mortality with treatment
## Transplacental Drugs for VT and TdP

<table>
<thead>
<tr>
<th>AA Agent</th>
<th>F:M drug ratio</th>
<th>Efficacy acute and chronic</th>
<th>Intraamniotic accumulation</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Magnesium Sulfate</strong></td>
<td>1:1(+)</td>
<td>80+%, Baseline high</td>
<td></td>
<td>CNS</td>
</tr>
<tr>
<td>Class</td>
<td>IV, PO Co-admin Vit D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Propranolol, Other BB</strong></td>
<td>0.25:1</td>
<td>Partial, ↓QTc, lowers Vfib risk</td>
<td>2-4X</td>
<td>Brady, Nadolol concentrates in breast milk</td>
</tr>
<tr>
<td>Class C</td>
<td>IV, PO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lidocaine/Mexiletine</strong></td>
<td>0.5:1</td>
<td>50+%</td>
<td>0.5-1.0</td>
<td>CNS, Paradox ↑QTc</td>
</tr>
<tr>
<td>Na ch Inhib</td>
<td>IV/PO</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Drugs to treat VT with NI QTc, Not Torsades de Pointes**

| Flecainide                | 1:1            | 60%                         | 27X serum level            | CNS, brady, ↑QTc                                |
| Na Inhib                  |                |                             |                            |                                                   |
| Class C                   |                |                             |                            |                                                   |
| **Sotalol**               | 0.9:1(+)       | 50-60%                      | 28X serum level            | CNS, brady, ↑QTc                                |
| K Inhib/B bl. Class B     |                |                             |                            |                                                   |
| **Amiodarone**            | 0.4:1, long-term after loading | 90+%                      | All tissues                | Brady, no breast feeding                         |
| Class D                   |                |                             |                            |                                                   |
Knowledge Gaps and Research Barriers

- Fetal cardiac monitoring and drug monitoring
- Education
- Research Recruitment
  - Limited enrollment of non-English speaking subjects and minors
  - Complicated site set up
- Access to postnatal follow up records arduous
  - Institution-specific release-of-information forms
  - Costs, delays
  - Separation of ECG’s from the EMR
- Other Barriers: Institutions unwilling to take on costs and Industry partners unwilling to take on the risk
Suggestions for Improving Fetal Drug and Device Research Translation

- Federally-funded Consortium for Fetal Drugs and Devices (modelled after the FDA Pediatric Device Consortium)
- Prospective data registry for antiarrhythmic agents in pregnancy
- Prospective international collaborative clinical trials

Kogutt et al. JObGyn 2020
Thank you